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# State Estimation in Type 2 Diabetes Using The Continuous-Discrete Unscented Kalman Filter<sup>\*</sup>

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**Abstract:** Using a nonlinear model for the glucose-insulin dynamics in type 2 diabetes, formulated in continuous-time as a stochastic differential equation, we seek to estimate the system states and parameters based only on discrete-time self-monitored blood glucose measurements of fasting glucose and the known exogenous insulin dose. This is done by means of continuous-discrete unscented Kalman filtering. The results are compared to an implementation of a continuous-discrete extended Kalman filter. Simulations show that it is possible to estimate all states with good accuracy using the CD-UKF, while it is also possible to estimate one unknown parameter at the same time. Further simulations show that increasing the sample rate makes it possible to estimate more parameters, given that the meal intake of the patient is known perfectly.

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**Keywords:** Type 2 Diabetes, Continuous-Discrete State Estimation, Unscented Kalman Filter

## 1. INTRODUCTION

Diabetes is a chronic disorder which prevents the body from naturally regulating the blood glucose level. We usually distinguish between type 1 diabetes (T1D) and type 2 diabetes (T2D). In non-diabetic people, the pancreas produces insulin to lower the glucose level, but in T1D patients no insulin is produced at all, while T2D patients may have a lowered production rate or insufficient response to insulin, which results in elevated glucose levels.

Too high glucose levels, called hyperglycemia, can lead to long-term complications such as cardiovascular diseases, while too low glucose levels, called hypoglycemia, can have immediate consequences such as coma or, in very severe cases, death.

T2D can usually be treated by changing to a healthier diet and by doing more physical exercise, but if this is not sufficient, insulin treatment is also an option, typically through long-acting insulin injected before breakfast. The treatment goal is to reach a safe level of fasting blood glucose level, i.e., the blood glucose level in the morning, of typical 4-5 mmol/L.

Because each T2D patient is different, it is difficult to choose the right insulin dose needed for the patient to reach the target glucose level. The process of adjusting the dose until a specific target glucose level is reached is called titration. As a too high dose may cause hypoglycemia, doctors have to be careful not to increase the dose too much, which in general results in the titration period being very long.

This titration may possibly be improved by applying closed-loop control to decide the insulin dose. In order to realize this in an optimal manner, knowledge about the states of the system is important.

A lot of research has gone into state estimation in T1D. This is among others used for closed-loop control within the research area of artificial pancreases and for calculating pre/post meal insulin injection doses. For instance, Eberle and Ament (2011) has compared different Kalman filter approaches for estimating plasma insulin concentration evaluated on clinical data, while Szalay et al. (2014) in a simulation study investigates the use of different sigma-point methods for estimating different states in the T1D model, both showing good results when using the discrete unscented Kalman filter (UKF). In a simulation study by Boiroux et al. (2017), the continuous-discrete unscented Kalman filter (CD-UKF) is used to estimate states as well as the parameter describing insulin sensitivity for calculating meal-time insulin injections, and latest, Boiroux et al. (2019) has applied a maximum likelihood approach using the continuous-discrete extended Kalman filter (CD-EKF) to estimate various parameters, both studies based on continuous glucose monitor (CGM) measurements.

However, in T2D, research related to state and parameter estimation is less prevalent. Aradóttir et al. (2017) has, based on a typical T1D model augmented with endogenous insulin production, proposed a model for the insulin-glucose dynamics in T2D, in which some parameters are estimated by Aradóttir et al. (2018) using a maximum likelihood approach based on sparse clinical data.

In this paper, we seek to investigate state and parameter estimation in this T2D model further. As the UKF and CD-UKF previously have shown good results when used

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on T1D models, we will investigate this further by applying a new method for computing the CD-UKF, as proposed by Knudsen and Leth (2019). The main contribution of this paper is that, based on simulations, we show that, using this method, it is possible to estimate all states successfully based only on fasting glucose measurements, as well as the possibility of estimating some parameters without having to use maximum likelihood methods.

The rest of the paper is organized as follows. In section 2, the investigated model describing the insulin-glucose dynamics in T2D is presented. In section 3-5, the main results are presented.

## 2. THE INVESTIGATED MODEL

### 2.1 Insulin-Glucose Dynamics in T2D

This paper will be based on the model for glucose-insulin dynamics in T2D suggested in Aradóttir et al. (2017). The model is given as follows:

$$\dot{I}_{sc}(t) = 1/(\tau_1 C_I) U(t) - 1/\tau_1 I_{sc}(t), \quad (1a)$$

$$\dot{I}_p(t) = 1/\tau_2 I_{sc}(t) - 1/\tau_2 I_p(t), \quad (1b)$$

$$\dot{I}_{eff}(t) = p_2 S_I (I_p(t) + I_{endo}(t)) - p_2 I_{eff}(t), \quad (1c)$$

$$\dot{G}(t) = -(G_{EZI} + I_{eff}(t)) G(t) + E_{GP} + R_A. \quad (1d)$$

Equation (1a) and (1b) describe how the injected insulin  $U(t)$  diffuses from the subcutaneous compartment  $I_{sc}(t)$  (the tissue just under the skin) to the blood plasma compartment  $I_p(t)$ . The characteristics of this diffusion depends on the insulin absorption time constants  $\tau_1$  and  $\tau_2$ , as well as the insulin clearance rate  $C_I$ , which describes how much plasma is cleared of insulin per time unit. The magnitude of the time constants depends on which kind of insulin is used, e.g., whether it is long-acting or fast-acting insulin.

Equation (1c) and (1d) of the model describe how insulin affects the blood glucose level  $G(t)$ . The insulin effect is modelled by  $I_{eff}(t)$ , such that when  $I_{eff}(t)$  is positive, the rate of change in blood glucose concentration will decrease. The magnitude of the effect depends on the gain given by the insulin sensitivity  $S_I$  of the patient. When the plasma insulin concentration  $I_p(t)$  increases, the insulin does not take immediate effect, which is described by the delay given by the inverse time constant  $p_2$ .

Unlike T1D patients, T2D patients also have an endogenous insulin production. This is taken into account through the term  $I_{endo}(t)$ , which is modelled as

$$I_{endo}(t) = S_G G(t), \quad (2)$$

where  $S_G$  is a constant that can be interpreted as glucose sensitivity of the insulin producing cells in the pancreas.

When at zero insulin, the rate at which the glucose concentration is lowered still depends on the current glucose concentration. This is accounted for by the parameter  $G_{EZI}$ , which represents the effect of glucose to lower endogenous glucose production at zero insulin. The endogenous glucose production itself is represented by the parameter  $E_{GP}$ , and the rate of glucose appearing due to food ingestion is contained within  $R_A$ .

To describe food ingestion (or orally ingested carbohydrates), the following second-order model is used:

$$\dot{D}_1(t) = 1000/M_{wG} d(t) - 1/\tau_m D_1(t), \quad (3a)$$

$$\dot{D}_2(t) = 1/\tau_m D_1(t) - 1/\tau_m D_2(t), \quad (3b)$$

where  $D_1(t)$  and  $D_2(t)$  are two meal compartments,  $d(t)$  is the rate of glucose consumption,  $M_{wG}$  is the molar weight of glucose and  $\tau_m$  is the time constant corresponding to meal absorption. This is included in the model (1) by inserting

$$R_A = D_2(t)/(V_G \tau_m), \quad (4)$$

where  $V_G$  is the glucose distribution volume, i.e. the volume of the part of the body in which the glucose is distributed.

### 2.2 Parameter Values

Values for all the different parameters in (1) have not previously been directly estimated for T2D patients. However, in Aradóttir et al. (2018) some parameters have been estimated based on sparse data sets from T2D patients. Due to the low sampling frequency of at most one sample per day, it is difficult to estimate all gains and time constants. Therefore, they instead estimated parameters by rewriting the model using the following substitutions:

$$\begin{aligned} \tilde{I}_{sc} &= I_{sc} C_I, & \tilde{I}_p &= I_p C_I, & \tilde{I}_{eff} &= I_{eff} C_I / S_I, \\ \tilde{S}_I &= S_I / C_I, & \tilde{\beta} &= S_G C_I, & \tau_1 &= \tau_2. \end{aligned}$$

This results in the following model, which is the one we will investigate in the sequel:

$$\dot{\tilde{I}}_{sc}(t) = 1/\tau_1 U(t) - 1/\tau_1 \tilde{I}_{sc}(t), \quad (5a)$$

$$\dot{\tilde{I}}_p(t) = 1/\tau_1 \tilde{I}_{sc}(t) - 1/\tau_1 \tilde{I}_p(t), \quad (5b)$$

$$\dot{\tilde{I}}_{eff}(t) = p_2 (\tilde{I}_p(t) + \tilde{\beta} G(t)) - p_2 \tilde{I}_{eff}(t), \quad (5c)$$

$$\dot{G}(t) = -(G_{EZI} + \tilde{S}_I \tilde{I}_{eff}(t)) G(t) + E_{GP} + D_2(t)/(V_G \tau_m), \quad (5d)$$

$$\dot{D}_1(t) = 1000/M_{wG} d(t) - 1/\tau_m D_1(t), \quad (5e)$$

$$\dot{D}_2(t) = 1/\tau_m D_1(t) - 1/\tau_m D_2(t). \quad (5f)$$

In this model, values of all parameters have previously been estimated in one way or another. The parameter  $\tau_1$  is assessed based on knowledge about long-acting insulin in Aradóttir et al. (2018),  $p_2$  and  $G_{EZI}$  are estimated based on clinical data from T1D patients in Kanderian et al. (2009),  $\tilde{S}_I$ ,  $E_{GP}$  and  $\tilde{\beta}$  are estimated based on clinical data from T2D patients in Aradóttir et al. (2018) and  $\tau_m$  and  $V_G$  are based on data in Wilinska et al. (2010). The parameter values can be found in Table 1 and these are the parameter values we use to simulate the system.

Table 1. Parameter values for (5).

	Value	Unit
$\tau_1$	0.5	[day]
$p_2$	15.8	[1/day]
$\tilde{S}_I$	1.80	[1/U]
$G_{EZI}$	3.31	[1/day]
$E_{GP}$	368	[mmol/L/day]
$\tilde{\beta}$	1.68	[U L/mmol/day]
$\tau_m$	0.026	[day]
$V_G$	22	[L]

### 2.3 The Model in a Stochastic Setting

**Process noise** The fasting glucose level in T2D patients is not the same each day. This may both be due to external factors such as exogenous insulin and meal intake, but some of it is also simply due to biological variability, which is best modelled as a stochastic process.

The day-to-day variability of fasting blood glucose in newly diagnosed T2D patients has been shown to be around 14% (Ollerton et al. (1999)). A useful way of introducing this variability is by formulating the model as a stochastic differential equation (SDE), i.e.,

where  $\mathbf{x} = [\tilde{I}_{sc} \ \tilde{I}_p \ \tilde{I}_{eff} \ G \ D_1 \ D_2]^T$ ,  $\mathbf{u} = [U \ d]^T$ ,  $f$  is the function corresponding to the right-hand side of (5) and  $\mathbf{w}_t \in \mathbb{R}^6$  is a standard Wiener process, i.e.,  $\mathbf{w}_t \sim \mathcal{N}(0, \mathbf{I}t)$ . The diffusion term  $\sigma \in \mathbb{R}^{6 \times 6}$  is chosen to be a constant matrix, and hence independent of  $\mathbf{x}$ . No specific values for  $\sigma$  is found in the literature. Instead,  $\sigma$  has been tuned such that the coefficient of variation (CV) of fasting glucose in the simulation is 14%. Choosing  $\sigma$  as twice the identity matrix has been shown to accomplish this.

**Measurement noise** For T2D patients, it is standard medical procedure for the patient to measure the blood glucose in the morning before breakfast, usually through finger-pricking. This results in so-called self-monitored blood glucose (SMBG) data of fasting glucose levels. This measurement can be modelled simply as a discrete-time sample of the state  $x_4(t) = G(t)$  in the model with some measurement noise. The measurement function is thus given as

$$y(t_k) = x_4(t_k) + v(t_k), \quad (6)$$

where  $t_k$  is the time of the measurement and  $v(t_k)$  is white Gaussian noise with variance  $R(t_k)$ . The ISO 15197 standard requires devices used for SMBG measurements to have an accuracy of  $\pm 20\%$  for glucose levels above 4.2 mmol/L and an accuracy of  $\pm 0.83$  mmol/L for glucose levels below 4.2 mmol/L, compared to more advanced laboratory measurements. This may be reasonably approximated by setting  $R(t_k) = 1$ .

**Generating the input** When simulating the system, the following assumptions are made regarding the inputs. An insulin dose of 30 U is given every day at 07:00 in the morning, simulated as an impulse.

The meal intake is assumed to consist of three major meals and three smaller snacks, also simulated as impulses. The size of each meal is uniformly distributed with a variance of 30, with the means adding up to a total of 410 g daily ingested carbohydrates.

### 3. SIMULATION RESULTS WITH KNOWN PARAMETERS

We first test the CD-UKF on the system when all parameters are known. For details regarding the CD-UKF, see Knudsen and Leth (2019).

The system is simulated using the Euler-Maruyama method with a discretization time step of 2 minutes. For estimating states in the T2D model, the CD-EKF and CD-UKF has been implemented in MATLAB<sup>®</sup>. The tuning

parameters for the UT has been chosen to be  $\alpha = 1$  and  $\kappa = 2$ , yielding  $\lambda = 2$  (see Grewal and Andrews (2008) for notation). The number of subsamples in the CD-UKF are 45. The insulin input is known, while the meal intake is considered as an unmeasured disturbance and therefore considered to be 0.

In the following,  $\tilde{\mathbf{x}}^+ = \mathbf{x}_{k+1} - \hat{\mathbf{x}}_{k+1|k+1}$  is used to denote the a posteriori state estimation error and  $\tilde{y}^- = y_{k+1} - \hat{y}_{k+1|k}$  is used to denote the a priori output estimation error or innovation.

In Table 2, the root mean squared (RMS) error of the a posteriori state estimates and the innovation are shown. These values are the mean as well as standard deviation of 100 simulation runs for a time period of 50 days.

In Fig. 1 and 2, data from one realization is shown for the CD-UKF.

Table 2. RMS error values for 100 simulation runs.

	Mean RMS						
	$\tilde{x}_1^+$	$\tilde{x}_2^+$	$\tilde{x}_3^+$	$\tilde{x}_4^+$	$\tilde{x}_5^+$	$\tilde{x}_6^+$	$\tilde{y}^-$
CD-UKF	1.09	1.21	1.00	0.25	0.25	0.30	1.04
CD-EKF	1.08	1.23	1.00	0.25	0.25	0.30	1.05
	Standard deviation of RMS						
	$\tilde{x}_1^+$	$\tilde{x}_2^+$	$\tilde{x}_3^+$	$\tilde{x}_4^+$	$\tilde{x}_5^+$	$\tilde{x}_6^+$	$\tilde{y}^-$
CD-UKF	0.12	0.12	0.10	0.03	0.02	0.03	0.11
CD-EKF	0.11	0.12	0.11	0.03	0.02	0.03	0.10

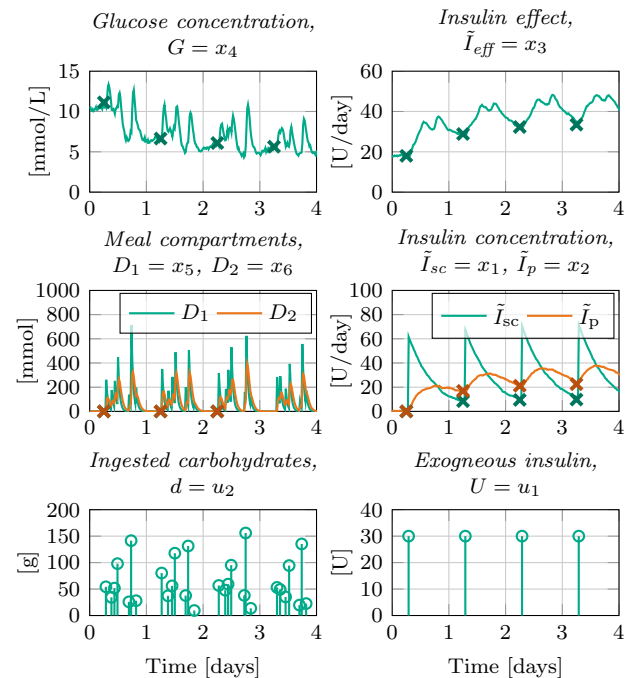


Fig. 1. Example of state estimation compared to the actual continuous-time state evolution. The crosses indicate the estimated values.

The accuracy of the state estimation is in general good. The innovation sequence is seen to be white based on the autocorrelation function (ACF) shown in Figure 2. A portmanteau lack-of-fit test confirms this with significance level 0.95, indicating that the estimation is close to

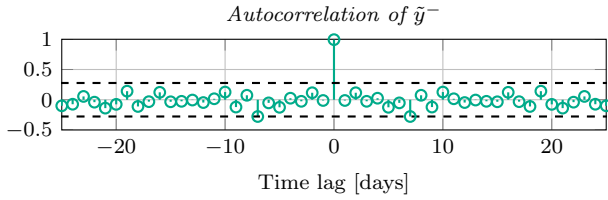


Fig. 2. ACF of the innovation. The dashed lines indicate the 95% confidence interval for white noise.

optimal. Based on the 100 simulation runs, it is seen that there is no significant difference in the accuracy of the state estimation between the CD-UKF and the CD-EKF. The computation time has, however, been observed to be on the order of 30 times larger for the CD-UKF compared to the CD-EKF. This is due to the high number of subsamples in the CD-UKF time update, which is a necessity when the measurement sampling time is as long as it is, i.e., one sample per day.

As mentioned earlier, the meal intake is not taken into account in the Kalman filter and it would therefore be expected that the estimation error regarding  $D_1$  and  $D_2$  would be large. However, as we are considering *fasting* glucose measurements, the meal compartments are expected to be empty at the time of observation. This is indeed the case, and the estimated value for the meal compartments at this time should therefore always be zero, resulting in a low estimation error. If the glucose measurement instead is performed at a non-fasting time, e.g., at noon, the estimation would be far off as the filter has no information about the patient eating lunch.

#### 4. PARAMETER ESTIMATION USING CD-UKF

Having shown that it is possible to estimate the states of the T2D system using the CD-UKF, we next investigate whether it is possible to estimate the parameters as well. The simplest approach is to model the parameters as a Wiener process and augment the state vector with the parameter, giving an SDE on the form

$$d \begin{bmatrix} \mathbf{x}_t \\ \boldsymbol{\theta}_t \end{bmatrix} = \begin{bmatrix} f(\mathbf{x}_t, \boldsymbol{\theta}_t, \mathbf{u}_t) \\ \mathbf{0} \end{bmatrix} dt + \begin{bmatrix} \boldsymbol{\sigma} & \mathbf{0} \\ \mathbf{0} & \boldsymbol{\sigma}_\theta \end{bmatrix} d\tilde{\mathbf{w}}_t, \quad (7)$$

where  $\boldsymbol{\theta}$  is the vector of parameters to estimate,  $\boldsymbol{\sigma}_\theta$  is the diffusion matrix specific to the parameters and  $\tilde{\mathbf{w}}_t$  is the augmented standard Wiener process. We assume that the initial state error covariance is of the form  $\tilde{\mathbf{P}}_{0|0} = \begin{bmatrix} \mathbf{P}_x & \mathbf{0} \\ \mathbf{0} & \mathbf{P}_\theta \end{bmatrix}$ .

Initial conditions may be handled in different ways. It seems reasonable to choose the initial values based on some a priori knowledge about the distribution of the parameter to estimate. For instance, if the parameter  $\theta$  is known beforehand to be distributed as  $\theta \sim \mathcal{N}(\mu, \sigma^2)$ , it would be natural to choose the initial mean value to be  $\hat{\theta}_{0|0} = \mu$ .

In the following, we take the opposite approach. For illustrative purposes, we keep the value of the parameters in the model to always be the same (see Table 1 on page 2 for the parameter values) and instead either choose (deterministically) our initial mean or draw it from a probability distribution.

*Estimation of a single parameter at a time* As a starting point, we attempt to estimate each parameter one at a time based only on SMBG measurements of fasting glucose. Examples of the time evolution of the parameter estimates are shown in Figure 3. Simulations for four different initial mean values  $\hat{\theta}_{0|0}$  are shown for each parameter, where the four different initial mean values are chosen symmetrically about the actual parameter value, such that two are close to the actual value and two are farther away. In all simulations, the parameter is modeled with zero diffusion, i.e.,  $\sigma_\theta = 0$ , resulting in  $d\theta_t = 0$ . As the estimates are slow to converge, the system is simulated for 1000 days.

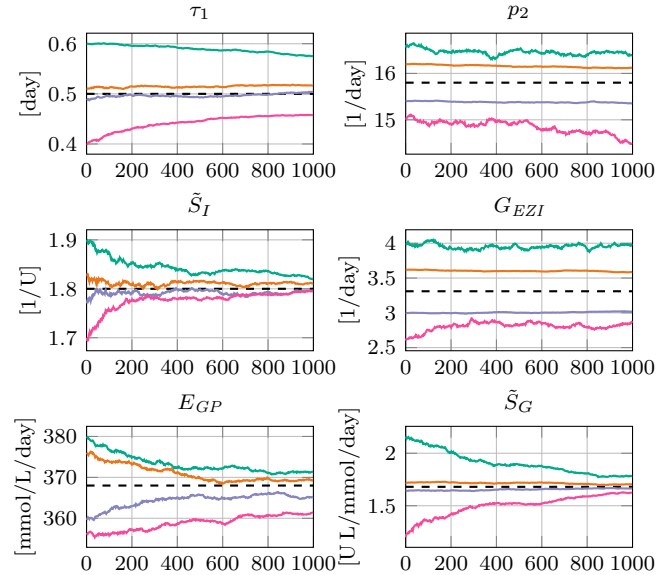


Fig. 3. Time evolution of parameter estimates for four different initial conditions when estimating a single parameter at a time. The dashed line indicates the true parameter value.

From these examples, it is evident that only the estimates of  $\tilde{S}_I$ ,  $E_{GP}$  and  $\tilde{S}_G$  converge to the actual parameter value. These observations agree with the results by Aradóttir et al. (2018), where values for  $\tilde{S}_I$ ,  $E_{GP}$  and  $\tilde{S}_G$  were estimated based on sparse clinical data using a maximum likelihood approach.

*Estimation of several parameters at a time* In the following, we investigate whether these three parameters can be estimated at the same time using only the CD-UKF.

For  $\boldsymbol{\theta} = [\tilde{S}_I \ E_{GP} \ \tilde{S}_G]^T$ , the initial mean value  $\hat{\boldsymbol{\theta}}_{0|0}$  is drawn from a normal distribution with mean  $\boldsymbol{\mu}_\theta = [1.80 \ 368 \ 1.68]^T$  and covariance

$$\mathbf{C}_\theta = \text{diag}(0.07^2, 4^2, 0.07^2).$$

The initial error state covariance is chosen to be  $\mathbf{P}_\theta = \text{diag}(0.025^2, 3^2, 0.025^2)$ . The diffusion is assumed zero.

For brevity, no examples are shown for this case. In general, how the estimation evolves seems to depend heavily on the initial condition and none of the parameter estimates seem to converge to the actual parameter values. These tendencies are the same when estimating only two



parameters at a time, i.e., the remaining parameter is known.

*Remark:* In the CD-UKF time update, when the sigma points are propagated through the system, the integration may risk diverging if the sigma points are not sufficiently close to the true value, e.g., if a sigma point corresponding to a time constant is negative. In the simulations so far, this problem has been addressed by choosing  $\mathbf{P}_\theta$  sufficiently small, which may be the cause of the slow convergence. This problem is less pronounced when the sampling time is shorter, which we will address in the following.

## 5. INCREASING THE SAMPLING RATE

To estimate parameters related to faster dynamics, a faster sampling time is needed, which furthermore would make the parameter estimation converge faster as more measurements would be processed.

While it is not uncommon for T1D patients to continuously monitor their blood glucose throughout the day, it is more rare for T2D patients to do so. Nevertheless, we here consider a faster sampling rate in order to assess whether more samples is of any use. Specifically, we consider a case equivalent to a continuous glucose monitor (CGM), where the blood glucose is continuously monitored with a sampling time of 6 minutes.

When estimating states and parameters based on non-fasting glucose measurements, the meal intake will have to be taken into account as well. So far, the meal intake has been considered as an unmeasured disturbance, which has little to no impact when observing at a fasting time. While it in this simulation study is possible to simply consider it as a known input instead, it may be an unrealistic assumption in practice, as it would require the patient to note down the time and size of every meal. Nevertheless, we here investigate the case where the meal intake is known perfectly.

As before, we first take a look at estimating just one parameter at a time. Some examples of the time evolution of the parameter estimates are shown in Figure 4. For  $\tau_1$ ,  $p_2$ ,  $\tilde{S}_I$ ,  $G_{EZI}$  and  $\tilde{S}_G$ , the initial state error covariance is set to  $P_\theta = 0.1^2$  while for  $E_{GP}$  and  $\tau_m$  it is set to  $P_\theta = 10^2$  and  $P_\theta = 0.03^2$ , respectively.

Here it can be seen that with the higher sampling rate, it is possible to estimate all parameters except  $p_2$  and  $G_{EZI}$ . Most notably, with a sampling time this fast, it is now possible to estimate the time constants  $\tau_1$  and  $\tau_m$  as well as the glucose distribution volume  $V_G$ . Additionally, compared to the results in Figure 3, the estimates converge significantly faster (note the different time axes), which is not surprising as there is a lot more information available in a short amount of time.

Next, we investigate whether some parameters can be estimated at the same time. As it is too much work to test every single combination of parameters, we confine ourselves to just look at all parameters, except  $p_2$  and  $G_{EZI}$ , at the same time. We employ the same approach as in Section 4.0.2, where we draw our initial mean from a probability

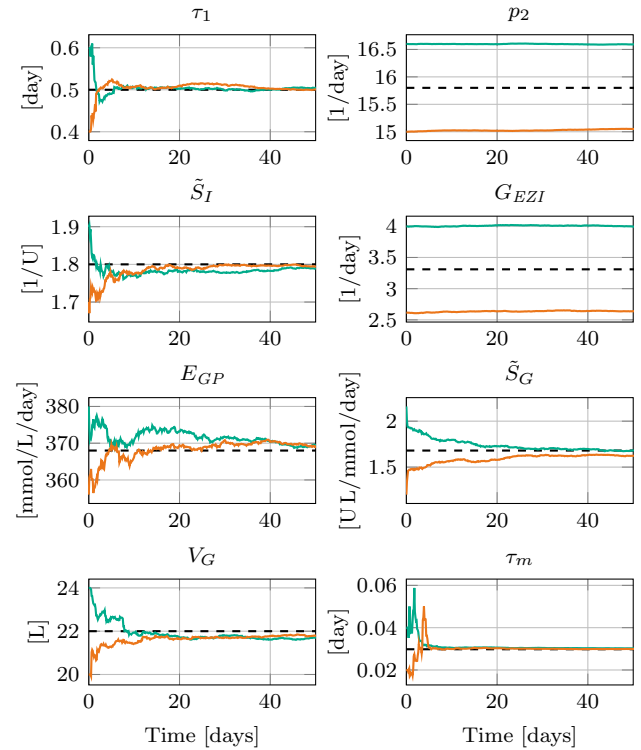


Fig. 4. Time evolution of parameter estimates for different initial conditions when estimating a single parameter at a time with a sampling time of  $T_s = 6$  min.

distribution. For  $\theta = [\tau_1 \ \tilde{S}_I \ E_{GP} \ \tilde{S}_G \ V_G \ \tau_m]^T$ , the initial mean value  $\hat{\theta}_{0|0}$  is drawn from a normal distribution with mean  $\mu_\theta = [0.5 \ 1.80 \ 368 \ 1.68 \ 22 \ 0.03]^T$  and covariance  $\mathbf{C}_\theta = \text{diag}(0.1^2, 0.1^2, 5^2, 0.1^2, 1^2, 0.72^2)$ . We use  $\mathbf{P}_\theta = \mathbf{C}_\theta$ . Some examples of this are shown in Figure 5.

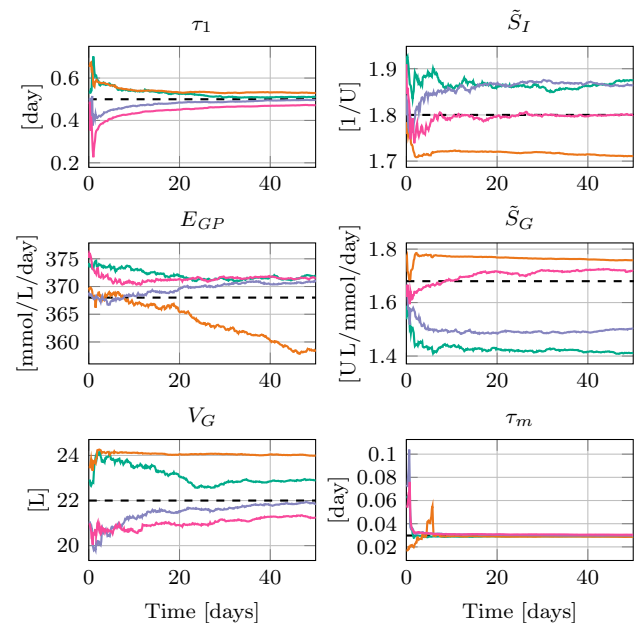


Fig. 5. Time evolution of parameter estimates when estimating all parameters except  $p_2$  and  $G_{EZI}$  at the same time when sampling with  $T_s = 6$  min.

It can here be seen that only the time constants  $\tau_1$  and  $\tau_m$  consistently converge to the actual parameter value, while the remaining parameters do not. This may be due to the fact that these two time constants each constitute an individual subsystem directly related to an (in this case known) input, namely the insulin compartmental subsystem and the meal compartmental subsystem. Although not shown here, having the remaining parameters, namely  $p_2$  and  $G_{EZI}$ , be uncertain does not change the convergence of  $\tau_1$  and  $\tau_m$ . These results thus suggest that using the CD-UKF it is possible to estimate  $\tau_1$  and  $\tau_m$  based on continuously monitored glucose measurements and known insulin and meal intake, but with no specific knowledge about the remaining parameters. To the best of the authors' knowledge, this result is novel.

Based on these observations, it does not seem far-fetched to think that one or two other parameters may be estimated along with the time constants. This is indeed the case, as may be seen in Figure 6. For brevity, the estimates of  $\tau_1$  and  $\tau_m$  are only shown for the case of the third parameter being  $\tilde{S}_I$ , but the behavior is similar for the three other cases investigated.

From Figure 6, it is seen that it is possible to estimate  $\tau_1$ ,  $\tau_m$  and one other parameter being either  $\tilde{S}_I$ ,  $E_{GP}$ ,  $\tilde{S}_G$  or  $V_G$ . It has not been tested whether it is possible to estimate any other combinations of parameters.

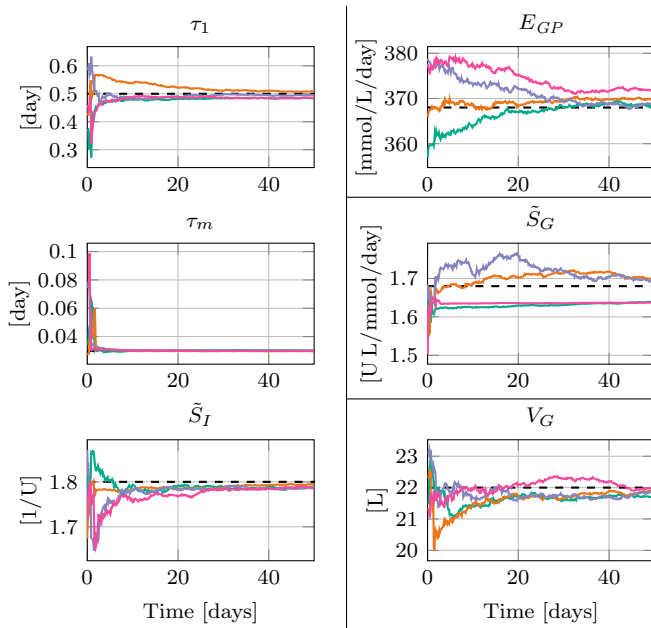


Fig. 6. Left: Estimate of  $\tau_1$ ,  $\tau_m$  and  $\tilde{S}_I$ . Right (upper; middle; lower): Estimate of  $\tau_1$ ,  $\tau_m$  (not shown): and  $E_{GP}$ ; and  $\tilde{S}_G$ ; and  $V_G$ .

## 6. CONCLUSION

Based on simulations of a model describing the insulin-glucose dynamics in T2D, it has been shown that, using a recently developed method for computing the CD-UKF, it is possible to estimate all system states satisfactorily using only fasting glucose measurements and known insulin injections. Additionally, it was shown to be possible to estimate one unknown parameter, the parameter being either

the insulin sensitivity  $\tilde{S}_I$ , endogenous glucose production  $E_{GP}$  or glucose sensitivity of the insulin producing cells in the pancreas  $\tilde{S}_G$ , using only the CD-UKF.

Increasing the sampling rate to match CGM data and assuming the meal intake is known perfectly made it possible to estimate additional parameters with a faster convergence rate.

These results may be useful for on-line parameter estimation in advanced control strategies such as control based on linear parameter-varying (LPV) models.

In future work, the results presented here will have to be verified on clinical data as well.

## REFERENCES

- Aradóttir, T., Boiroux, D., Bengtsson, H., Kildegaard, J., Orden, B., and Jørgensen, J. (2017). Model for simulating fasting glucose in type 2 diabetes and the effect of adherence to treatment. In *IFAC-PapersOnLine*, volume 50, 15086–15091. Elsevier.
- Aradóttir, T., Boiroux, D., Bengtsson, H., and Poulsen, N. (2018). Modelling of fasting glucose-insulin dynamics from sparse data. In *Proceedings of 40th International Conference of the IEEE Engineering in Medicine and Biology Society*, 2354–57. IEEE.
- Boiroux, D., Mahmoudi, Z., and Jrgensen, J. (2019). Parameter estimation in type 1 diabetes models for model-based control applications. In *2019 American Control Conference (ACC 2019)*.
- Boiroux, D., Aradóttir, T., Nørgaard, K., Poulsen, N., Madsen, H., and Jørgensen, J. (2017). An adaptive nonlinear basal-bolus calculator for patients with type 1 diabetes. *Journal of Diabetes Science and Technology*, 11(1), 29–36.
- Eberle, C. and Ament, C. (2011). The unscented Kalman filter estimates the plasma insulin from glucose measurement. *Biosystems*, 103(1), 67 – 72.
- Grewal, M.S. and Andrews, A.P. (2008). *Kalman Filtering: Theory and Practice Using MATLAB®*. John Wiley & Sons, Inc., 3 edition.
- Kanderian, S.S., Weinzimer, S., Voskanyan, G., and Steil, G.M. (2009). Identification of intraday metabolic profiles during closed-loop glucose control in individuals with type 1 diabetes. *Journal of Diabetes Science and Technology*, 3(5), 1047–1057.
- Knudsen, T. and Leth, J.J. (2019). A new continuous discrete unscented Kalman filter. *IEEE Transactions on Automatic Control*.
- Ollerton, R.L., Playle, R., Ahmed, K., Dunstan, F.D., Luzio, S.D., and Owens, D.R. (1999). Day-to-day variability of fasting plasma glucose in newly diagnosed type 2 diabetic subjects. *Diabetes Care*, 22(3), 394–398.
- Szalay, P., Molnar, A., Muller, M., Eigner, G., Rudas, I., Beny, Z., and Kovcs, L. (2014). Comparison of sigma-point filters for state estimation of diabetes models. In *Conference Proceedings - IEEE International Conference on Systems, Man and Cybernetics*, volume 2014.
- Wilinska, M.E., Chassin, L.J., Acerini, C.L., Allen, J.M., Dunger, D.B., and Hovorka, R. (2010). Simulation environment to evaluate closed-loop insulin delivery systems in type 1 diabetes. *Journal of diabetes science and technology*, 4 1, 132–44.